533 Rec'd PCT/PTO 08 DEC 2000

FORM PTO-1390 (REV 12-29-99) U.S. DEPARTMENT OF COMMERCE PATENT AND TRADEMARK OFFICE

TRANSMITTAL LETTER TO THE UNITED STATES DESIGNATED/ELECTED OFFICE (DO/EO/US) CONCERNING A FILING UNDER 35 U.S.C. 371

ATTORNEY'S DOCKET NUMBER: PT-1877000

U.S. APPLICATION NO. (If known, see 37 CFR 1.5): 09/719142

INTERNATIONAL APPLICATION NO.	INTERNATIONAL FILING DATE	PRIORITY DATE CLAIMED
PCT/CA99/00541	June 10/99 (06/10/99)	June 15/98 (06/15/98)

TITLE OF INVENTION: PHARMACEUTICAL TABLETS COMPRISING AN NSAID AND A PROSTAGLANDIN

APPLICANT(S) FOR DO/EO/US: BERNARD CHARLES SHERMAN

Applicant herewith submits to the United States Designated/Elected Office (DO/EO/US) the following items and other information:

1. [X] This is a **FIRST** submission of items concerning a filing under 35 U.S.C. 371.
2. [ ] This is a **SECOND or SUBSEQUENT** submission of items concerning a filing under 35 U.S.C. 371.
3. [X] This express request to begin national examination procedures (35 U.S.C. 371(f)) at any time rather than delay examination until the expiration of the applicable time limit set in 35 U.S.C. 371(b) and PCT Articles 22 and 39(1).
4. [X] A proper Demand for International Preliminary Examination was made by the 19th month from the earliest claimed priority date.
5. [X] A copy of the International Application as filed (35 U.S.C. 371(c)(2))
   a. [X] is transmitted herewith (required only if not transmitted by the International Bureau).
   b. [ ] has been transmitted by the International Bureau.
   c. [ ] is not required, as the application was filed in the United States Receiving Office (RO/US).
6. [ ] A translation of the International Application into English (35 U.S.C. 371(c)(2)).
7. [ ] Amendments to the claims of the International Application under PCT Article 19 (35 U.S.C. 371(c)(3))
   a. [ ] are transmitted herewith (required only if not transmitted by the International Bureau).
   b. [ ] have been transmitted by the International Bureau.
   c. [ ] have not been made; however, the time limit for making such amendments has NOT expired.
   d. [ ] have not been made and will not be made.
8. [ ] A translation of the amendments to the claims under PCT Article 19 (35 U.S.C. 371(c)(3)).
9. [X] An oath or declaration of the inventor(s) (35 U.S.C. 371(c)(4)).
10. [ ] A translation of the annexes to the International Preliminary Examination Report under PCT Article 36 (35 U.S.C. 371(c)(5)).

Items 11. to 16. below concern document(s) or information included:

11. [X] An Information Disclosure Statement under 37 CFR 1.97 and 1.98.
12. [ ] An assignment document for recording. A separate cover sheet in compliance with 37 CFR 3.28 and 3.31 is included.
13. [ ] A FIRST preliminary amendment.
    [ ] A SECOND or SUBSEQUENT preliminary amendment.
14. [ ] A substitute specification.
15. [ ] A change of power of attorney and/or address letter.
16. [X] Other items or information:
    - Certified copy of Canadian Patent No. 2,241,342

533 Rec'd PCT/PTO 08 DEC 2000

US APPLICATION NO (if known, see 37 CFR 1.5)	INTERNATIONAL APPLICATION NO	ATTORNEY'S DOCKET NUMBER
09/719142	PCT/CA99/00541	PT-1877000

17. ☐ The following fees are submitted:

BASIC NATIONAL FEE (37 CFR 1.492 (a) (1) - (5)):	CALCULATIONS PTO USE ONLY
Neither international preliminary examination fee (37 CFR 1.482) nor international search fee (37 CFR 1.445(a)(2)) paid to USPTO and International Search Report not prepared by the EPO or JPO $1,000.00	
International preliminary examination fee (37 CFR 1.482) not paid to USPTO but International Search Report prepared by the EPO or JPO $860.00	
International preliminary examination fee (37 CFR 1.482) not paid to USPTO but international search fee (37 CFR 1.445(a)(2)) paid to USPTO $710.00	
International preliminary examination fee paid to USPTO (37 CFR 1.482) but all claims did not satisfy provisions of PCT Article 33(1)-(4) $690.00	
International preliminary examination fee paid to USPTO (37 CFR 1.482) and all claims satisfied provisions of PCT Article 33(1)-(4) $100.00	
ENTER APPROPRIATE BASIC FEE AMOUNT =	$ 860.00
Surcharge of $130.00 for furnishing the oath or declaration later than ☐ 20 ☐ 30 months from the earliest claimed priority date (37 CFR 1.492(e)).	$ ----

CLAIMS	NUMBER FILED	NUMBER EXTRA	RATE	
Total claims	20 - 20 =	-----	X $18.00	$ ----
Independent claims	1 - 3 =	-----	X $80.00	$ ----
MULTIPLE DEPENDENT CLAIM(S) (if applicable)			+$270.00	$ 270.00
TOTAL OF ABOVE CALCULATIONS =				$ 1,130.00
Reduction of 1/2 for filing by small entity, if applicable. A Small Entity Statement must also by filed (Note 37 CFR 1.9, 1.27, 1.28).				$
SUBTOTAL =				$ 1,130.00
Processing fee of $130.00 for furnishing the English translation later than ☐20 ☐30 months from the earliest claimed priority date (37 CFR 1.492(f)). +				$
TOTAL NATIONAL FEE =				$
Fee for recording the enclosed assignment (37 CFR 1.21(h)). The assignment must be accompanied by an appropriate cover sheet (37 CFR 3.28, 3.31). $40.00 per property +				$
TOTAL FEES ENCLOSED =				$ 1,130.00
			Amount to be: refunded	$
			charged	$

a. ☒ A check in the amount of $ 1,130.00 to cover the above fees is enclosed.

b. ☐ Please charge my Deposit Account No. _____ in the amount of $_____ to cover the above fees. A duplicate copy of this sheet is enclosed.

c. ☒ The Commissioner is hereby authorized to charge any additional fees which may be required, or credit any overpayment to Deposit Account No. 08-3255. A duplicate copy of this sheet is enclosed.

NOTE: Where an appropriate time limit under 37 CFR 1.494 or 1.495 has not been met, a petition to revive (37 CFR 1.137(a) or (b)) must be filed and granted to restore the application to pending status.

SEND ALL CORRESPONDENCE TO.

SIGNATURE

Neil H. Hughes, P.Eng
NAME

33,636
REGISTRATION NUMBER

IN THE UNITED STATES PATENT OFFICE

Application Serial No. (To be Assigned)

(Based on International Application Number PCT/CA99/00541 filed on June 10, 1999)

Our Ref: PT-1877000
CUSTOMER NO. 23607

Applicant: Bernard Charles Sherman

Agent: Neil H. Hughes
Suite 200
175 Commerce Valley Drive West
Thornhill, Ontario
Canada, L3T 7P6

Title: PHARMACEUTICAL TABLETS COMPRISING AN NSAID AND A PROSTAGLANDIN

Inventor: Bernard Charles Sherman

Due Date: December 15, 2000

PRELIMINARY AMENDMENT

December 7, 2000

The Commissioner of Patents
UNITED STATES PATENT OFFICE
2011 South Clark Place
Crystal Plaza 2, Room 1B03
Arlington, Virginia, U.S.A. 22202

Dear Sir:

By way of Preliminary Amendment Applicant respectfully requests that the following submissions be entered.

IN THE DISCLOSURE

No changes.

IN THE CLAIMS

Please amend the claim set as set out below consistent with the PCT filing and the amendment of May 25, 2000 (attached) filed in response to the Written Opinion of March 30, 2000. The claims have been placed in proper format for U.S. prosecution to avoid improper multiple dependencies. The subject matter of claims 1 to 11 is identical to the subject matter of claims 1 to 7 in the PCT amended claim set dated May 25, 2000.

The following claims therefor stand in the application:

1. A pharmaceutical tablet comprising a shell in which is imbedded two smaller tablets covered by material of the shell of the pharmaceutical tablet, one of which tablet comprises an NSAID and the other of which tablets comprises misoprostol, whereby the two smaller tablets are not exposed to the environment of the surface of the pharmaceutical tablet.

2. The pharmaceutical tablet of Claim 1 wherein the smaller tablet containing the NSAID is enteric coated.

3. A pharmaceutical tablet as in Claim 1 or 2 wherein the NSAID is piroxicam.

4. A pharmaceutical tablet as in Claim 1 or 2 wherein the NSAID is selected from diclofenac and salts thereof.

5. A pharmaceutical tablet as in Claim 3 wherein the amount of piroxicam is from about 10 mg to about 20 mg.

6. A pharmaceutical tablet as in Claim 4 wherein the amount of diclofenac or a salt thereof is from about 25 mg to about 75 mg.

Please amend the claim as follows:

7. (Amended) The [A] pharmaceutical tablet [as in any] of Claim[s] [1 to 6] 1 or 2 wherein the amount of misoprostol is about 200 μg.

Please add the following claims:

8. The pharmaceutical tablet of Claim 3 wherein the amount of misoprostol is about 200 μg.

9. The pharmaceutical tablet of Claim 4 wherein the amount of misoprostol is about 200 μg.

10. The pharmaceutical tablet of Claim 5 wherein the amount of misoprostol is about 200 μg.

11. The pharmaceutical tablet of Claim 6 wherein the amount of misoprostol is about 200 μg.

REMARKS

If there should occur an overpayment or an underpayment of fees in respect of this application, the Commissioner is authorized to access Deposit Account Number 08-3255 to make the appropriate adjustments.

If the Examiner has any questions, the Examiner is respectfully requested to contact Neil H. Hughes at (905) 771-6414 collect at his convenience.

Respectfully submitted,

Neil H. Hughes
Agent for the Applicants
Registration No. 33,636

NHH:mse
Enclosure

PHARMACEUTICAL TABLETS COMPRISING AN NSAID AND A PROSTAGLANDIN

BACKGROUND OF THE INVENTION

The invention herein is directed to a pharmaceutical tablet which comprises both an NSAID and misoprostol.

Nonsteroidal anti-inflammatory drugs (NSAIDs) comprise a class of drugs which have long been recognized as having high therapeutic value especially for the treatment of inflammatory conditions such as exhibited in inflammatory diseases like osteoarthritis and rheumatoid arthritis. While the NSAIDs present a beneficial therapeutic value, they also exhibit undesirable side effects. An especially undesirable side effect of the administration of NSAIDs is the ulcerogenic effects generally associated with chronic use. NSAID induced ulcers in the stomach can be dangerous. Such ulcers generally exhibit few or no symptoms and may cause dangerous bleeding when undetected. In some instances, bleeding ulcers can prove fatal.

Certain prostaglandins have been shown to prevent NSAID induced ulcers. Misoprostol is a prostaglandin which has been accepted for use in the treatment of NSAID induced ulcers in many countries, including the United States.

It is desirable to provide a pharmaceutical composition which exhibits the beneficial properties of an NSAID and which also exhibits the beneficial properties of misoprostol for countering the ulcerogenic side effects attendent to NSAID administration.

This can be achieved by combining an NSAID and misoprostol in a single pharmaceutical tablet. However this in not easy to do, because misoprostol is highly unstable, and it is thus desirable not to have the misoprostol and NSAID mixed together, so as to prevent any deleterious effect of the NSAID on the stability of the misoprostol.

One solution to this problem, which is disclosed in US Patent 5601843, is to produce a tablet consisting of an inner core which comprises the NSAID and a mantle which surrounds the inner core and comprises the misoprostol. It is also disclosed that, in order to prevent contact between the misoprostol and the NSAID at the surface of the inner core, the inner core may be coated with an inert coating. Such coating may be an enteric coating, which also serves to reduce the likelihood of the NSAID dissolving in the stomach and thereby prevent exposing the stomach to the NSAID.

While the invention of US Patent 5601843 accomplishes its objective of separating the NSAID from the misoprostol, it has certain disadvantages. One disadvantage is the need to have a coating on the inner core in order to completely prevent contact between the NSAID in the inner core and the misoprostol in the mantle.

A second disadvantage is that the misoprostol is dispersed throughout the mantle, and is thus exposed to the environment at the surface of the tablet. This exposure increases the vulnerability of the misoprostol to degradation due to the effects of light or atmospheric oxygen and moisture.

The object of the present invention is to enable a pharmaceutical tablet that incorporates both an NSAID and misoprostol, but overcomes these disadvantages.

BRIEF SUMMARY OF THE INVENTION

The present invention is a pharmaceutical composition in the form of a tablet in which two smaller tablets are embedded, one of which comprises an NSAID and the second of which comprises misoprostol.

DETAILED DESCRIPTION OF THE INVENTION

Pharmaceutical tablets are routinely made on a tablet press. In the tabletting process, a mixture of materials in the form of a free flowing powder or granular mix is filled into a metal die, into which a metal punch protrudes from beneath. A second metal punch is then inserted into the die from above, and pressure is applied to the upper and lower punches to cause the powder or granular mix to be compressed into a tablet. The upper punch is then withdrawn, and the tablet is ejected from the die by raising the lower punch further into the die.

Compositions (i.e. tablets) of the present invention may be made as follows:

1. Firstly, a tablet comprising the NSAID and a tablet comprising the misoprostol are made in separate tabletting operations. The portion of the composition which surrounds the two smaller tablets will be referred to herein as the "shell".

2. Then the final composition is assembled in a further tabletting operation as follows:

   (i) Part of the powder or granular mix of which the shell is to be comprised is filled into the die, into which a punch has been inserted from below.

(ii) One of the smaller tablets comprising the NSAID and one of the smaller tablets comprising the misoprostol are then inserted into the die.

(iii) The balance of the powder or granular mix of which the shell is to be comprised is then filled into the die to cover two smaller tablets.

(iv) The upper punch is then inserted into the die from above and pressure is applied between the punches to compress the powder or granular mix around the two smaller tablets into the form of the final tablet.

(v) The upper punch is then withdrawn and the lower punch is raised further into the die to eject the composition.

The NSAID contained within one of two smaller tablets will preferably be piroxicam or diclofenac or a salt of diclofenac such as diclofenac sodium or diclofenac potassium. Most preferably, the NSAID will be diclofenac sodium.

Where diclofenac or a salt thereof is used, the amount per tablet will preferably be from 25 to 75 mg. The tablet containing diclofenac or salt thereof will contain, along with the diclofenac or salt thereof, usual tablet excipients such as binders, lubricants, fillers and the like. Preferably, the tablet containing the diclofenac or salt thereof will be coated with an enteric film coating to prevent the diclofenac or salt thereof from dissolving until after it has passed through the stomach and entered the small intestine. The enteric coating can be formulated with any suitable enteric coating polymer, many of which are known to those skilled in the art.

Where piroxicam is used as the NSAID, the amount per tablet will preferably be 10 to 20 mg. Again the tablet containing piroxicam will also comprise usual tablet excipients.

The tablet containing the misoprostol will also include, along with the misoprostol, usual tabletting excipients. The misoprostol will preferably be used in the form of a dispersion in hydroxypropyl methylcellulose, which is known in the prior art to improve the stability of misoprostol. The quantity of misoprostol per tablet will preferably be about 200 μg.

The shell which surrounds the tablet containing the NSAID and the tablet containing the misoprostol will be comprised of usual tablet excipients, without any active medicinal ingredient mixed therein.

The invention will be further understood from the following example, which is intended to be illustrative and not limiting of the scope of the invention.

EXAMPLE 1

Tablets containing diclofenac sodium are made with a composition as follows:

	Amount per tablet
Diclofenac sodium	50.0 mg
Microcrystalline cellulose	24.0 mg
Magnesium stearate	1.0 mg
Croscarmellose sodium	5.0 mg
	80.0 mg

These cores are then optionally enteric coated by spraying onto them a suspension or solution of an enteric coating polymer and a plasticizer.

EXAMPLE 2

Tablets containing misoprostol are made with a composition as follows:

	Amount per tablet
Misoprostol 1% dispersion in hydroxypropyl methylcellulose	20.0 mg
Microcrystalline cellulose	8.5 mg
Magnesium stearate	0.5 mg
Croscarmellose sodium	1.0 mg
	30.0 mg

EXAMPLE 3

A powder mix for producing the shell of the final tablet is prepared as a mixture of 99.5% by weight microcrystalline cellulose and 0.5% magnesium stearate.

EXAMPLE 4

The final composition is then made by making tablets from the mix of Example 3 and embedding in each such tablet one tablet from Example 1 and one tablet from Example 2, by the procedure previously described; that is to say, using a tablet press equipped to insert one tablet from Example 1 and one tablet from Example 2 as well as a quantity of the powder mix for the shell from Example 3 into a die, and making the final tablet by compression between a lower punch and a upper punch inserted into the die from below and above respectively.

CLAIMS:

1. A pharmaceutical tablet comprising a shell in which is imbedded two smaller tablets covered by material of the shell of the pharmaceutical tablet, one of which tablet comprises an NSAID and the other of which tablets comprises misoprostol, whereby the two smaller tablets are not exposed to the environment of the surface of the pharmaceutical tablet.

2. The pharmaceutical tablet of Claim 1 wherein the smaller tablet containing the NSAID is enteric coated.

3. A pharmaceutical tablet as in Claim 1 or 2 wherein the NSAID is piroxicam.

4. A pharmaceutical tablet as in Claim 1 or 2 wherein the NSAID is selected from diclofenac and salts thereof.

5. A pharmaceutical tablet as in Claim 3 wherein the amount of piroxicam is from about 10 mg to about 20 mg.

6. A pharmaceutical tablet as in Claim 4 wherein the amount of diclofenac or a salt thereof is from about 25 mg to about 75 mg.

7. A pharmaceutical tablet as in any of Claims 1 to 6 wherein the amount of misoprostol is about 200 μg.

PTO/SB/01 (12-97)
Approved for use through 9/30/00. OMB 0651-0032
Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE
Under the Paperwork Reduction Act of 1995, no persons are required to respond to a collection of information unless it contains a valid OMB control number.

DECLARATION FOR UTILITY OR DESIGN PATENT APPLICATION (37 CFR 1.63)			
☒ Declaration Submitted with Initial Filing	OR	☐ Declaration Submitted after Initial Filing (surcharge (37 CFR 1.16 (e)) required)	

Attorney Docket Number	PT-1877000
First Named Inventor	Bernard Charles Sherman
COMPLETE IF KNOWN	
Application Number	/
Filing Date	
Group Art Unit	
Examiner Name	

As a below named inventor, I hereby declare that:

My residence, post office address, and citizenship are as stated below next to my name.

I believe I am the original, first and sole inventor (if only one name is listed below) or an original, first and joint inventor (if plural names are listed below) of the subject matter which is claimed and for which a patent is sought on the invention entitled:

PHARMACEUTICAL TABLETS COMPRISING AN NSAID AND A PROSTAGLANDIN

the specification of which

☐ is attached hereto
OR

☒ was filed on **(MM/DD/YYYY)** 06/10/1999 as United States Application Number or PCT International Application Number PCT/CA99/00541 and was amended on **(MM/DD/YYYY)** _____ (if applicable).

I hereby state that I have reviewed and understand the contents of the above identified specification, including the claims, as amended by any amendment specifically referred to above.

I acknowledge the duty to disclose information which is material to patentability as defined in 37 CFR 1.56.

I hereby claim foreign priority benefits under 35 U.S.C. 119(a)-(d) or 365(b) of any foreign application(s) for patent or inventor's certificate, or 365(a) of any PCT international application which designated at least one country other than the United States of America, listed below and have also identified below, by checking the box, any foreign application for patent or inventor's certificate, or of any PCT international application having a filing date before that of the application on which priority is claimed.

Prior Foreign Application Number(s)	Country	Foreign Filing Date (MM/DD/YYYY)	Priority Not Claimed	Certified Copy Attached? YES	Certified Copy Attached? NO
2,241,342	CANADA	06/15/1998	☐	☒	☐
			☐	☐	☐
			☐	☐	☐
			☐	☐	☐

☐ Additional foreign application numbers are listed on a supplemental priority data sheet PTO/SB/02B attached hereto:

I hereby claim the benefit under 35 U.S.C. 119(e) of any United States provisional application(s) listed below.

Application Number(s)	Filing Date (MM/DD/YYYY)	☐ Additional provisional application numbers are listed on a supplemental priority data sheet PTO/SB/02B attached hereto.

PTO/SB/01 (12-97)
Approved for use through 9/30/00. OMB 0651-0032
Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE
Under the Paperwork Reduction Act of 1995, no persons are required to respond to a collection of information unless it contains a valid OMB control number.

DECLARATION - Utility or Design Patent Application

I hereby claim the benefit under 35 U.S.C. 120 of any United States application(s), or 365(c) of any PCT international application designating the United States of America, listed below and, insofar as the subject matter of each of the claims of this application is not disclosed in the prior United States or PCT International application in the manner provided by the first paragraph of 35 U.S.C. 112, I acknowledge the duty to disclose information which is material to patentability as defined in 37 CFR 1.56 which became available between the filing date of the prior application and the national or PCT international filing date of this application.

U.S. Parent Application or PCT Parent Number	Parent Filing Date (MM/DD/YYYY)	Parent Patent Number *(if applicable)*

☐ Additional U.S. or PCT international application numbers are listed on a supplemental priority data sheet PTO/SB/02B attached hereto.

As a named inventor, I hereby appoint the following registered practitioner(s) to prosecute this application and to transact all business in the Patent and Trademark Office connected therewith:

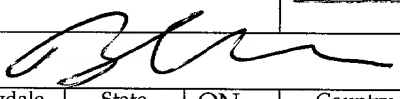
☒ **Customer Number 23607**

Direct all correspondence to: **Customer Number 23607.**

I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under 18 U.S.C. 1001 and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

Name of Sole or First Inventor: ☐ A petition has been filed for this unsigned inventor

Given Name (first and middle [if any])	Family Name or Surname
BERNARD CHARLES	SHERMAN

Inventor's Signature	 CAX					Date	Dec 5, 2000
Residence: City	Willowdale	State	ON	Country	Canada	Citizenship	CA
Post Office Address	50 Old Colony Road						
Post Office Address							
City	Willowdale	State	ON	ZIP	M2L 2K1	Country	CA

☐ Additional inventors are being named on the _____ supplemental Additional Inventor(s) sheet(s) PTO/SB/02A attached hereto.